Can genetic discoveries revolutionise bowel cancer care?

Behind the Genes Transcript

**Helen: Welcome to Behind the Genes.**

**Ian:** One of the great hopes is that some of these new genes that we’ve found could be useful in preventing cancer and it doesn’t necessarily matter that they’re rare, even if they’re only 1% of cancers, by using those and changing those in the normal individual before they have had cancer then we may be able to reduce that risk. So, there are lots of potential new targets for prevention that are coming through.

**My name is Helen White and I’m the Participant Panel Vice-Chair for Cancer at Genomics England. Today I’m delighted to be joined by Professor Ian Tomlinson, Professor of Cancer Genetics at the University of Oxford, Claire Coughlan, Clinical Lead for Bowel Cancer UK and consultant nurse in colorectal cancer, and Dr David Church, a clinical scientist fellow and a medical doctor specialising in oncology at Oxford University.**

**Today we will be discussing a pioneering colorectal cancer study which using data from the 100,000 Genomes Project has uncovered new insights that could transform diagnosis and treatment for patients with bowel cancer. If you enjoyed today’s episode we would love your support, please like, share and rate us on wherever you listen to your podcast.**

**Thank you for joining me today. We’re going to be discussing the findings from a landmark study that has been published in nature. This study used data generously donated by people with bowel cancer who took part in the 100,000 Genomes Project giving us the most detailed look yet at the genetic makeup of colorectal cancer better known as bowel cancer. But before we get into that let’s start by hearing from my guests. Could each of you please introduce yourselves.**

**Ian:** I’m Ian Tomlinson, I work at the University of Oxford and most of my work is research into bowel cancer, it’s genetic causes, the genes that are involved in actually causing the cancer to grow which may be different from genetic causes and also the use of that data to help patients whether guiding future treatments or potentially helping to prevent bowel cancer which would obviously be our optimum strategy to have the biggest impact on the disease and its incidents.

**Claire:** So, I’m Claire Coughlan, I’m the clinical lead for Bowel Cancer UK and my remit at the charity is to ensure that everything we do is clinically relevant and that we’re providing services that meet the needs of those affected by bowel cancer and the educational needs of those health professionals that work with people affected by bowel cancer. I’m also a nurse consultant in colorectal cancer at Lewisham and Greenwich NHS Trust and I lead an urgent referral service there and also work with patients with late effects of bowel cancer.

**David:** I’m David Church, I’m a medical oncologist and Cancer Research UK advanced clinician scientist at the University of Oxford. I treat bowel cancer clinically and do research on bowel cancer and womb cancer including a lot of research using samples and data from Genomics England data service we’re discussing today of course.

**Helen: Great, thank you. Now let’s turn to Claire to learn more about bowel cancer. Claire, can you share with us how common it is, how treatable it is and if there are any trends in terms of which groups of people are affected?**

**Claire:** Of course, bowel cancer is a relatively common cancer, there are about 46,000 people each year in the UK diagnosed with bowel cancer so that is quite a large number. The thing that really drives us forward in bowel cancer is that the earlier stage you’re diagnosed at the greater chance of survival. So, the figures for that are quite stark, we stage bowel cancer through stage one to 4 with one being the earliest stage and 4 being the most advanced.

If you are diagnosed with bowel cancer at stage one you have a 9 in 10 chance of being alive and well 5 years after your diagnosis of bowel cancer. And if you’re diagnosed at the other end of the spectrum at stage 4 that drops to a 1 in 10 and should people survive after a diagnosis of stage 4, which more people than before do they will have had a lot of treatment for their bowel cancer so the burden of the treatment will also be with them after that. So, it’s really important that we diagnose at the earliest possible stage which is why studies such as the one we’re going to talk about today are so important.

We have noticed that there has been a slight increase in being diagnosed at a younger age. That said the latest statistic is 2,600 people were diagnosed under the age 50 in the UK last year so it’s still a disease of older people, you still have a greater chance of getting bowel cancer as you get older but it’s really, really important that we’re aware that you can still get bowel cancer as a younger person.

Probably one of the most exciting things that has happened for bowel cancer of recent years is our bowel cancer screening programme and the age for that now has been brought down to 50, we’re not quite there all over the country, but in the UK that is the aim that everyone will be screened for bowel cancer at the age of 50. So, yes it’s a common disease and staging an early detection is vital.

**Helen: That’s lovely Claire, thank you very much for that. David, turning to you could you please explain to us how bowel cancer typically develops?**

**David:** Yes, so we know compared with many cancer types quite a lot about how bowel cancer develops because the bowel is accessible to collect samples by a technique called endoscopy which is putting a camera into the bowel from which you can sample tumours or lumps. And so from genetic research done in the last 10 years we know that, or we’ve known for many years actually, for much longer, that cancer is a genetic disease, it’s a disease caused by alterations in genes and particularly genes that control whether the cells in our bowel grow normally and die normally as they should do.

And collectively when there are alterations in genes that regulate those processes you can have a cell or collection of cells which are able to grow without restraint and don’t die when they should do which are some of the hallmarks of a cancer and they also require the ability to spread elsewhere in the body which is what kills people with cancer including bowel cancer. We know from research done in the last 10 to 15 years that some of the alterations in genes that can cause bowel cancer in combination occur very early in our life, even in the first and second decade of life, but don’t cause cancer.

The earliest detectable abnormality is typically a polyp which is a tumour, a lump within the bowel which is detectable and if removed is almost certainly cured by removal alone but if it’s not detected then as that grows and acquires more alterations in genes then it can become a cancer and cancers develop the ability to invade the bowel wall, to spread to what we call lymph nodes or glands nearby and also to spread further afield, most commonly to the liver or to the lungs.

And for most people whom bowel cancer has spread to the liver or to the lungs or elsewhere unfortunately we’re not able to cure their disease which as Claire has said is why there is such an importance in detecting cancers and pre-cancers as we call them so that the tumours are not actually cancerous but come before bowel cancer as early as possible.

**Helen: Thank you David. Moving on to the study, Ian perhaps you can take this, in the study that you carried out my understanding is that the whole genome sequencing was used to investigate the genetic changes that lead to the development and growth of bowel cancer. And for this participants with bowel cancer in the 100,000 Genomes Project donated both a blood sample and a tumour sample while those with rare conditions only provided a blood sample, can you explain why that is?**

**Ian:** As you said the study really looked at 2 quite separate arms albeit with a little bit of overlap as we’ll see. So, one very important aim was to look at individuals, both children and adults, who had medical problems or other conditions that were unexplained but which had some features that suggested that they weren’t necessarily inherited but there may be some variation in their genes that had caused them, and roughly half of the programme was dedicated to that.

Within that there was a small number of people who had a strong family history of bowel cancer or who had large numbers of polyps in the bowel and they were analysed in a separate part of the project from what we’re mostly discussing. Within the cancer arm there was a collection really throughout England of patients who had most of the common types of cancer and a few with less common cancers.

And because when we’re looking at genetic and related changes in cancers we need to make sure that those changes have actually occurred in the cancer as it started growing from its earliest stages with a small number of cells in the body that were slightly abnormal and then progressing. We need to look at what genetic variation the patient has in all the cells of their body. We don’t want to look at patients and say that looks an interesting change, we may be able to use that if it’s present in all of the normal cells in that patient’s system.

We want to make sure the change is specific to the cancer itself and therefore we have to sequence both a sample probably taken from blood and a sample taken from the actual cancer. And in a way we subtract out the changes in the blood to identify the changes that have actually occurred in the cancer itself.

**Helen: That’s a very helpful explanation. Does this research show that there is a role for whole genome sequencing in clinical care?**

**Ian:** I think my own view is it is all a question of cost. I think the advantages it provides it can assess multiple types of genetic change at once. It is relatively consistent across each cancer’s genome between cancers, even between centres mean that it is the method of choice. There are undoubtedly developments that will happen in the future, maybe being able to sequence longer stretches of DNA in one go that will help the analysis.

And some of the computational methods are likely to develop to identify some of the slightly difficult to identify genetic changes but it ought to be the standard of choice. There are issues and potential difficulties in collecting the high-quality samples that have been needed from pathology laboratory and that will be difficult going forward with current budges and there are lots of challenges but ultimately it in some form has to be the method of choice. What wasn’t done is to look at other molecule tests or essays, looking at RNA wasn’t really done on a big scale as well as DNA and other changes to DNA apart from the genetic changes were not looked at.

So, there are certainly ways it could be improved if you had limitless money but I think the project, 100,000 Genomes has shown the whole genomes are. They have a lot of advantages and ultimately probably will be adopted by the NHS and similar organisations.

**Helen: David, could you now tell us about the findings of this pioneering study and what impact these findings might have on people with bowel cancer in the future?**

**David:** So, this is the largest study to date to analyse the entire genome of bowel cancer by some margin and the fact that we’ve done whole genome sequencing and in so many people it has really given us an unprecedented ability to identify the genetic alterations that drive bowel cancer. And within bowel cancer we’ve known for some time it is not a homogeneous entity that bowel cancer is not all created equal, that there are sub-groups of bowel cancer and we have been able to refine those over previous efforts. And I guess if you were to ask what the biggest take home for me from the study is it’s just the complexity of the disease.

So, as we’ve mentioned we know that cancer is a genetic disease, that it’s driven by genetic alterations, alterations in genes which regulate the growth of cells or the death of cells or the spread of cells. And we’ve known for many years that there is a modest number of genes which are commonly malfunctioning in bowel cancer and they would be in the tens to dozens really. But with this work we’ve hugely extended our understanding of the genes that drive bowel cancer and in fact we’ve discovered nearly 250 genes which are altered in bowel cancer and appear to drive the growth of the cancer.

Now we know that not all of those will be validated and by that I mean that there are associations that we find at the moment, not all of which will be biologically relevant but interpreted in the data we know a large number that are previously undiscovered are or we can be fairly confident of that. And one of the take homes from that is that many of these are only altered in a small fraction of bowel cancers.

So, rather than being perhaps half of bowel cancers or a third of bowel cancers there are a good number of genes, a very substantial number of genes, which are altered in say 3 to even 1% of bowel cancers. And if we think about how we go about targeting those and perhaps we’ll come onto treatment later that poses really challenges for how we work and we would think about treating patients with bowel cancer who have those particular alterations in their cancers.

**Helen: Thank you David, yes we’ll come onto treatment shortly, but I think Claire has a question for you.**

**Claire:** Yes, thank you. For me as somebody who works in this every day this is such an exciting and interesting study, particularly in light of what we said earlier about early detection and how critically important that is for improving outcomes in people with bowel cancer. So, in your view do you think this research could help shape future screening programmes or prevention strategies?

**David:** That’s a great question, I suppose in terms of screening at the moment the majority of screening is done in the UK at least by testing for blood in the stool which is relatively non-specific so I’m not sure that that would be directly impacted by this research. But one area of early cancer detection that is perhaps more relevant is quite a lot of work including from Oxford actually in recent years looking at blood tests. So, testing blood samples for early detection of cancer whereby you can test for genetic alterations, fragments of DNA that have alterations from the bowel cancer or any cancer that circulates in the blood and that tends to rely on a small number of common alterations.

And with this data I could see that we might be able to refine those tests and in so doing improve our early detection of cancer but that would need quite some work before we could actually say look that had real potential I think. And in terms of prevention there are, I think Ian may want to come in on this, one or 2 sub-groups which you might think that you could try to prevent but of course that needs a lot of extra work really.

But I think we have some clues of the biology of bowel cancer and particularly some of the sub-groups where you might think well this drug would work better in terms of preventing that sub-group or that sub-group but that will need to be the subject of future study.

**Helen: Ian, did you want to come in on that at all?**

**Ian:** So, at the moment prevention is a fairly new way of helping to reduce the number of people with bowel cancer at the level of the whole population which is what we have in the UK above a certain age group as we heard from Claire earlier. The methods used, again as we heard, are screening for occult blood in the stool and then colonoscopy to identify either hopefully early cancers or polyps and remove those. But when we think about the methods that we use for preventing other diseases then normally where they’re successful using a more easily delivered and I have to say less expensive method.

So, high blood pressure is treated to reduce the risk of cardiovascular disease and there are other diseases where those what you might call molecularly-based prevented strategies are coming in. We really lack that for bowel cancer in particular, it does happen for some other cancers, but one of the great hopes is that some of these new genes that we’ve found could be useful in preventing cancer. And it doesn’t necessarily matter that they’re rare, even if there are only 1% of cancers, by using those and changing those in a normal individual before they have had cancer then we may be able to reduce that risk.

So, there are lots of potential new targets for prevention that are coming through and as David said it is going to take a lot of work to work out which of those are deliverable and who will benefit. But we have quite a lot of opportunities in that space and although that may not be us that takes that forward, it may be, but it may not be. We think it is a lot of material for those interested in chemo prevention using drugs of cancer that they can work on and with luck deliver some new ways of preventing cancer that may be simply popping a pill every morning to take your risk right down to as close as zero as we can.

**Helen: Thank you Ian. David, I think you had something to add here.**

**David:** Thanks Helen. One area of prevention that we’re really interested in Oxford and many others are is using the genetic alterations that we find in bowel cancers and other cancers as targets for vaccination. Now we know that gene alterations will cause abnormal proteins which while they might drive the cancer, make it grow or not die, can also be recognised by the immune system so the abnormal proteins can be recognised by the immune system as being foreign and as foreign they can be targeted by the immune system so the immune system will try and kill the cells carrying those alterations. And we know for some sub-sets of bowel cancers those alterations can be relatively predictable actually, they occur in quite a sizeable fraction of some sub-groups of bowel cancers.

And one area that we’re particularly interested in at the moment and actively pursuing is using those targets where you need some additional work to demonstrate when they are particularly recognisable by the immune system. But to use these genetic alterations is potential targets for vaccination with the intention ultimately of preventing bowel cancer in at risk individuals or ideally in the full-term time the whole population. And we’ve received some funding from Cancer Research UK to pursue this line of research and we have a group working on this in Oxford and as I say many others do elsewhere.

**Helen: Thank you David, yes I have a vested interest in this because my understanding is this work is aimed primarily at people with a genetic condition called lynch syndrome which predisposes the people who have inherited this gene change alteration to bowel cancer, womb cancer and other cancer. And I had womb cancer, as I think David you know, a few years back and discovered it was due to lynch syndrome and so it’s really exciting that you’re now looking at vaccinating preventing because yes I take aspirin every day, I have my colonoscopy every 2 years which have some effect on preventing these cancers but it’s not 100% guaranteed. And I don’t suppose it ever will be but having the vaccination in that armoury would be fantastic I think for future generations, it’s very exciting and we look forward to hearing more about it.**

**Thank you Ian and David. I mean we’ve heard a lot there about preventing bowel cancer but I think moving back now to potential treatments, you know, we’ve heard from David how this study has shown a number of actionable findings but what are the next steps towards treatment? How can these findings be turned into real actions that will benefit those people diagnosed with bowel cancer in the future? Ian, perhaps you would like to pick up on this to start.**

**Ian:** That step is one, you know, in which I’m not personally an expert but a lot of the newer treatments are based on the finding of so called driving mutations which are simply genetic changes that occur as the cancer grows and contribute to that growth and ultimately if it’s not treated to the spread and dissemination of a cancer. And the fact that we have reported 250 which need validation but of which a large proportion are likely to be true drivers means that anyone of those can be a potential new target.

The criteria to be used for which of those mutations to pursue, which of those driver genes to chase up are quite complicated normally, depend on many things such as the interest of research groups and small and larger drug companies. And the similarity of those genes to other genes that have evolved and the processes that they make to go slightly wrong in the cancer.

So, there is also the issue that because these are uncommon, everybody talks a lot about personalised medicine or precision medicine, this would be truly precision or personalised medicine because a genetic change that was driving the cancer in only 1% of patients is obviously not a huge number of patients although bowel cancer is a common cancer so it’s not a tiny number either. But it would mean investment at that level to benefit let’s say 1 to 2% potentially of all patients with bowel cancer but I think that’s a nettle we have to grasp. And I think our results are showing that most of the really common drug changes either have not yet been successfully targeted in treatment or are too difficult to target.

So, we’re going to have to start looking at these less common genetic drivers and design strategies, inhibitors, you know, again that can be delivered to patients relatively straightforwardly in order to see whether they benefit the patients concerned. But there is this problem of getting enough patients enrolled in clinical trials where a change is only present in a relatively small proportion of all the patients with that cancer type.

**Helen: Thank you Ian. Presumably if there is a relatively small number of patients the people who are looking at running these trials might be looking at perhaps international trials, would that be one way to go?**

**Ian:** So, I think David can speak with more personal knowledge but there are international trial networks and there are collaborations along these lines already under way. I would hope that those could be made use of even more than they are already. There is, you know, a financial consideration for those developing new anticancer treatments which are, you know, high risk work and also the costs of setting up trials and enrolling people is not a trivial thing. So, I think those are hurdles that can be overcome but it would need a concerted effort to do that. Patients will play a major role in that and patient organisations as well as 100,00 Genomes and other similar projects.

**Helen: Yes, thank you, David I don’t know if you want to come in on that.**

**David:** Yes, the challenge of testing therapies in small groups is a very real one and there is lots of interest at the moment in exploring alternatives to conventional clinical trials. And as we use more electronic patient records and we have pharmacy records so there is the potential to get those data from routine clinical practice and there is lots of investments and attention on that at the moment so called real world data which is always an interesting term as if patients in clinical trials aren’t in the real world which of course they are.

But it’s perhaps a little more cost effective sometimes in clinical trials, of course it does pose its own challenges in how you disentangle true treatment effect from other factors because there are many factors impacting on how long people with cancer live. But there is a lot of investment and effort going into that at the moment and it will be interesting to see how that develops over the coming years.

**Helen: Turning to you Claire based on your experience how well do you think people with bowel cancer understand how genomes can help with their care and what support is currently available to them in this area?**

**Claire:** I think the answer, as it is so often is, it’s dependent on individuals and not just one individual. So, I think some patients are very motivated to know as much about this as possible and to understand and to know what the next steps may be in their own treatment that may be helped by this. Others don’t want to have the same knowledge and want to be guided very much by their medical teams but I think oncologists obviously are at the forefront of this and we see at the charity … we have services at the charity that supports patients and we see lots of queries into our ask the nurse service where people have been given variable information about I suppose personalised medicine as Ian alluded to and how their very specific bowel cancer may be treated, so I think it varies from patient to patient.

There is support available so we have the ask the nurse service I alluded to. We have a brilliant patient forum actually and everybody in clinical practice will have seen this, patients often become more expert than anybody and they share advice and they’re moderated forums that are a very safe place for people to ask questions where there is a moderator to ensure that it is made really clear that circumstances are individual.

And the same with the ask the nurse service because you don’t have all the clinical information so it is about empowering people, so there is support available. I think the other thing that is really important is equipping specialist nurses with the knowledge that they need to support their patients. This is a really exciting area of evolution for bowel cancer particularly I think in all cancers at the moment but for bowel cancer I think things have changed fairly rapidly in recent years and specialist nurses really need support in knowing that they have up-to-date information to give their patients.

So, that’s another challenge for us and any specialist nurses that might be listening to this podcast we have online education on genomics for specialist nurses. Just while we’re talking about that and you mentioned lynch syndrome earlier, so there has been a lynch syndrome project as I’m sure you’re aware where we’re trying to get testing for lynch syndrome brought into local hospitals.

So, there was some funding via NHS England so that the testing be done at time of diagnosis, so a pre-test and then a final test if that’s appropriate, for everybody diagnosed with bowel cancer to see if they have lynch syndrome. And in some trusts that has been done and in others it hasn’t yet and the funding hasn’t quite followed in the way that we need it to enable that to happen. It’s vitally important, we think there are about 175,000 people in the UK with lynch syndrome and we only know about 5% of them. And this is a gene change that is an inherited gene change so we can do what we call cascade testing where we test family members and we can then employ preventative strategies to prevent people from developing bowel cancer.

So, it’s a really important project, so I think as well as supporting patients with the information around the changes that are happening in this area we also need to ensure that we support the workforce and have investment there to enable the support of all the changes and the genomic landscape.

**Helen: Absolutely Claire and so much resonates there with what you’ve said. Having myself had cancer discovered that was due to lynch syndrome, cascade testing offered to my family members so valuable. It turns out I inherited my change from my mum who is 83, has never had cancer, so I think that’s a very good example of, you know, it doesn’t necessarily mean that you will get cancer but actually on that point that you made about empowering patients I always have a right smile because there is my mum going off to all her other medical appointments because at 83 she sees quite a few people and she is always the one telling them about lynch syndrome and educating them because most of them haven’t heard of it, so yes it’s really, really important.**

**And that patient forum, you’re probably aware of Lynch Syndrome UK, I don’t have any involvement in that other than being a member but that is so valuable for people with a particular condition to go somewhere where they can talk to or listen to other people with a similar condition, really, really valuable.**

**Right, well I think circling back really to the 100,000 Genomes Project I think you touched on this earlier David but reflecting on what you and Ian have told us about your study what is it about the 100,000 Genomes Project bowel cancer dataset that made this work possible?**

**David:** There are a few things, one of which and not least of which is the sheer size of the effort. So, to have whole genome sequencing. So, to have whole genome sequencing for more than 2,000 individuals is previously unprecedented and we’ll be seeing more of this now as we scale up our research efforts but at the inception of the project it was very, very ambitious and to be able to deliver that is a huge achievement. And the quality and breadth of the analysis is very strong as well.

And ultimately, you know, the former gives thanks to the people that were kind enough to donate samples to the 100,000 Genomes Project, they did so knowing that they almost certainly wouldn’t benefit personally from their donation from their gift and that any benefits would be some way down the line and hopefully benefit others which is what we’re seeking to realise now. But, you know, it’s not a given when we treat people in the clinic so we’re very, very grateful to those individuals.

And I think also to the scientists who worked incredibly hard over the last 5 years to deliver this work actually. So, having been part of the team and being lucky enough to be part of the team along with Ian we’ve had hugely motivated individuals that really have dedicated a large fraction of their working lives to delivering this project which I think is a fantastic achievement as well.

**Helen: Thank you, thank you to all those participants who at a time when their lives probably were turned completely upside down by a cancer diagnosis were offered the chance to join the 100,000 Genomes Project and said yes. As you say most of them will have known that it won’t have helped them but by donating their data, you know, it has allowed this work to happen and potentially it could change lots of people’s lives in the future, so thank you to them.**

**Ian:** Could I also just emphasise and agree with what David has said, I won’t go through all the individuals by name, but if anybody wants to read the published report of the work there are several people on there, Alex Cornish is the first author, but many colleagues from an institute of Cancer Research, The University of Manchester, Birmingham, Leeds, other universities in London that all contributed, but also colleagues in the NHS and/or universities who recruited patients, collected samples, processed them etc and of course the people who did the preparation of the samples in genetics laboratories and actually did the sequencing and basic analysis too.

So, it is a truly huge effort across particularly all the cancer types which is particularly a complex collection given the fact the tumour is needed and a blood sample. It’s quite difficult in a way to find a formal way of thanking them for all of this but without them it wouldn’t have happened.

**Helen: On that note I think we’ll wrap up there. A huge thank you to our guests, Professor Ian Tomlinson, Clare Coughlan and Dr David Church for an enlightening discussion on the groundbreaking study published in nature. This research is set to reshape our understanding of colorectal cancer and pave the way for new possibilities in treatment and patient care.**

**If you would like to hear more like this please subscribe to Behind the Genes on your favourite podcast app. Thank you for listening. I have been your host, Helen White. This podcast was edited by Bill Griffin at Ven2 Digital and produced by Naimah Callachand.**